Unusual Oxidation of 1-Halo-1,3-dienes with Permanganate. Expedient Syntheses of (+)-D-*chiro*-3-Inosose and (+)-D-*chiro*-Inositol from Chlorobenzene

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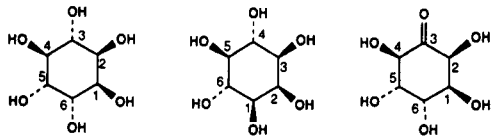
Demethylation of (+)-pinitol, obtained in modest amounts by extraction of sugar pine (*Pinas lambertiana* Dougl) wood dust[2] yields D-*chiro*-inositol (1), a potentially important compound in the treatment of diabetes.[3] While the therapeutic potential of D-*chiro*-inositol is immense, its availability is limited. In addition to the source mentioned above, it is also available by ether cleavage of the natural antibiotic kasugamycin.[4] D-*chiro*-Inositol might also be available by a possible enzymatic inversion of C-1 of the readily available *myo*-inositol (**2**)[3c] or by an enzymatic reduction of inosose (**3**).[5] In light of the



1, D-*chiro*-Inositol 2, *myo*-Inositol 3, D-*chiro*-3-Inosose

difficulties associated with obtaining large quantities of 1 in an economic fashion, a biocatalytic approach to 1 that would be competitive with the above processes was therefore deemed worthy of investigation.

The exploitation of cyclohexadiene *cis*-diols, originally discovered and described by Gibson 23 years ago,[6] in enantiocontrolled synthesis of oxygenated compounds is an area that has undergone an explosive growth in the last 5 years. Many applications to total synthesis of carbohydrates, cyclitols, and oxygenated alkaloids have appeared,[7] and the field is rapidly and successfully competing with the more traditional approaches of attaining optically pure compounds from the carbohydrate chiral pool.[8] A major part of our program in this area involves the application of precise symmetry-based planning to further functionalization of cyclohexadiene *cis*-diols of type **4** in enantiodivergent fashion, the most recent example of efficient execution of this goal being the synthesis of both enantiomers of pinitol in six synthetic operations from chlorobenzene via further oxidation of acetonide **5**.[9]

We sought an approach to the title compounds that would be environmentally benign as well as amenable to a multikilogram scale and this necessitated that a replacement for OsO_4, used in the previous preparation of diol **7**, be found. Furthermore, preliminary experiments in the opening of epoxide **8** with water suggested that little or no extrapolation can be made from our experience in ring-opening reactions of this compound with MeOH using acid or base catalysis.[9b] Hydrolysis of **8** proved extremely sensitive to precise conditions of the reaction and, unlike in the case of (+)-pinitol,[9] gave rise to more than one stereoisomer of the cyclohexane hexol.[10] A series of Payne rearrangements was invoked to explain why the outcome of epoxide opening proved to be nonspecific and led to other inositol isomers. We now wish to report preliminary solutions to these two problems as well as the preparation of **1** and **3**[11] from the unusual halo epoxy diol **6**, which is prepared by stereocontrolled oxidation of the halodiene in acetonide **5** with $KMnO_4$, Scheme I.

Diols **4**,[12] when treated with 2,2-dimethoxypropane/PTSA and exposed to 2 equiv of $KMnO_4/MgSO_4$ in aqueous acetone at −10° to 5 °C, gave an 8:1 mixture of diols **6a** and **7a** in 60% yield and **6b** and **7b** in the same ratio in 48% yield (isolated, recrystallized yield: **6a** = 32%; **6b** = 22%). Higher temperature and lower concentration of the reagent afforded the expected diol **7a** as the major product. The formation of **6a** is both unexpected and unusual based on the precedent in the literature regarding the lack of control in the oxidation of simple dienes with permanganate (two examples in low yield),[13] the known instability of α-halo epoxides,[14] and the unavailability of data concerning direct and controlled

(1) Recipient of the American Cyanamid Faculty Research Award, 1992.

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(3) (a) Kennington, A. S.; Hill, C. R.; Craig, J.; Bogardus, C.; Raz, I.; Ortmeyer, H. K.; Hansen, B. C.; Romero, G.; Larner, J. *N. Engl. J. Med.* **1990**, *323*, 373. (b) Huang, L. C.; Zhang, L.; Larner, J. *FASEB* **1992**, A1629 Abstr. # 4009. (c) Pak, Y.; Huang, L. C.; Larner, J. *FASEB* **1992**, A1629, Abstr. No. 4008. (d) Larner, J.; Huang, L. C.; Schwartz, C. F. W.; Oswald, A. S.; Shen, T.-Y.; Kinter, M.; Tang, G.; Zeller, K. *Biochem. Biophys. Res. Commun.* **1988**, *151*, 1416.

(4) Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M.; Takeuchi, T. *J. Antibiot. (Tokyo) Ser. A* **1965**, *18*, 101.

(5) Preliminary experiments with enzymatic reductions of **3** with commercial yeast alcohol dehydrogenase gave complex mixtures. Reductions of **3** with hydride reagents gave 3:1 mixtures of *allo*- and *chiro*-inositol.

(6) Cyclohexadiene *cis*-diols are obtained by oxidation of the corresponding arenes with whole cells of *Pseudomonas putida* strain 39/D (Biotype B organism), as previously described: Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626; Gibson, D. T.; Koch, G. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653. *P. putida* strain 39/D is obtained after mutagenesis of the organism with nitrosoguanidine. The organism therefore lacks the ability to process aromatic hydrocarbons beyond the first degradative step of the metabolic pathway. Other similar organisms have been prepared by the same procedure (U.S. Patent 4,508,822 and U.S. Patent 4,927,759) and although isolated from different sources, all of them produce *cis*-diols from aromatic compounds.

(7) For recent examples of the applications of arene diols to synthesis see: (a) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741. (b) Carless, H. A. J. *Tetrahedron Lett.* **1992**, 6379. (c) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2907. (d) Downing, W.; Latouche, R.; Pitoll, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Williams, J. O. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2613. (e) Boyd, D. R.; Dorrity, M. R. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J. Sheldrake, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 666. (f) Banwell, M. G.; Corbett, M.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1. (g) Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388. (h) Hudlicky, T.; Natchus, M. G. *J. Org. Chem.* **1992**, *57*, 4740. For comprehensive reviews of arene *cis*-diol chemistry see: (i) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chimica Acta* **1990**, *8*, 3. (j) Brown, S. M.; Hudlicky, T. *Organic Synthesis: Theory and Practice*; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113. (k) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795.

(8) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983.

(9) (a) Hudlicky, T.; Price, J. D.; Fan, R.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (b) Hudlicky, T.; Fan, R.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *31*, 229.

(10) Mandel, M.; Hudlicky, T. Unpublished observations.

(11) Although mentioned as a possible structure in the cyclitol literature, D-*chiro*-3-inosose has not been reported to our knowledge.

(12) (a) The diols derived from chloro- and bromobenzene are available crystalline and on a multikilogram scale from Genencor International, Inc., Rochester, NY, and from ICI Bioproducts, Manchester, U.K. (b) For a laboratory-scale (30–50 g) fermentation procedure using *Pp* 39 D mutant (obtained from Prof. D. T. Gibson University of Iowa), see: Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174.

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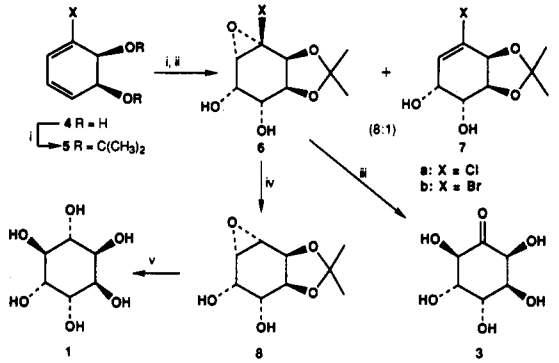
Scheme I. Synthesis of D-*chiro*-Inositol and D-*chiro*-3-Inosose



(i) DMP/PTSA; (ii) $KMnO_4/MgSO_4/H_2O$/acetone; (iii) Al_2O_3/H_2O; (iv) TTMSS/AIBN; (v) H_2O/sodium benzoate.

oxidation of 1-chloro-1,3-dienes with $KMnO_4$ or OsO_4.[7c] In preparative runs (20 g), this compound was prepared in one step by combining protection of **4a**[7c] with oxidation. Compounds **6** proved remarkably stable ($t_{1/2}$ of **6a** at 110 °C = approximately 50 h) and were transformed to the known epoxide 8[9] upon reduction with tris(trimethylsilyl)-silane/AIBN[15] in toluene in 42% yield (48% from **6b**). Both acid- and base-catalyzed conditions for hydrolysis of 8 were studied in detail[10] and led to the generation of mixtures of inositols containing D-*chiro*-inositol and *neo*-inositol in varying proportions. Ultimately, the opening and deprotection of this epoxide with water in the presence of a small amount of sodium benzoate at reflux gave nearly quantitative yield of product containing >95% of D-*chiro*-inositol. Recrystallization of the crude product gave 77% yield of pure D-*chiro*-inositol, identical with an authentic sample, based on mp, ^1H NMR, and optical rotation.

Direct hydrolysis of **6a** with water in the presence of Al_2O_3 furnished in high yield the rare inosose **3**, the reduction of which to 1 is being studied as a shorter alternative still to the preparation of D-*chiro*-inositol.[5] These results constitute a remarkably short and effective synthesis of D-*chiro*-inositol (1): three chemical operations, all but one of which are performed in aqueous media, with the fully controlled creation of six chiral centers.

Epoxide 8, prepared previously as an intermediate in the previously reported synthesis of (+)-pinitol by a procedure that involved the use of OsO_4,[9] need not be isolated during preparative scale runs. On a moderate scale (4 g of **6a**) this compound was produced with a reaction content of 65% and hydrolyzed directly to a mixture of inositols containing approximately 70% of D-*chiro*-inositol. Fractional crystallization of the title compound from such mixtures is possible, thereby precluding the use of chromatography in the entire synthesis. While the overall yield of 1 by this new procedure is only 13% in this preliminary protocol it avoids entirely the use of OsO_4 and chromatography.

The chemistry and indeed the unusual mechanism of the formation of halo epoxide **6** are being investigated in detail. It is clear that an attractive large scale preparation of 1 will ensue as a result of careful optimization, as will other applications to the synthesis of functionalized cyclitols and inositols, which are important along with certain phosphate derivatives in communication at the cellular level.[16] Such compounds and all of their derivatives can be prepared by controlled functionalization of arene *cis*-diols which are now available through biocatalysis on a commercial scale.[12,17] Further endeavors in this field will be reported in due course.

Experimental Section[18]

(1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-1-Chloro-3,4-dihydroxy-5,6-di-*O*-isopropylidene-1,2-epoxycyclohexane (6a). To a stirred solution of 1-chloro-2,3-dihydroxycyclohexa-4,6-diene (**4a**)[7h,12a,b] (20.0 g, 0.138 mol) in a mixture of dry acetone (210 mL) and 2,2-dimethoxypropane (23.8 mL, 0.194 mol), placed in a water bath, was added PTSA (0.80 g, 4.20 mmol). After 15 min was added saturated solution of Na_2CO_3 (10 mL) and the mixture was cooled to −5 °C (solution A). $KMnO_4$ (50.0 g, 0.316 mol) and $MgSO_4$ (21.0 g, 0.175 mol) were dissolved in water (1250 mL) and cooled to 5 °C (solution B). To a mixture of ice (250 g) and acetone (300 mL) cooled to −15 °C was added 50 mL of solution B. Then solutions A and B were simultaneously added during 25 min, maintaining a small excess of $KMnO_4$ in the reaction mixture and temperature under 5 °C. Precipitated MnO_2 was filtered off and washed with water and acetone. Resulting colorless solution was extracted with $CHCl_3$, the extract was dried and evaporated under reduced pressure to give 19.1 g of white solid containing 80% of **6a**. Recrystallization of the crude product from the mixture of EtOAc/hexane/Et_2O yielded in two crops 10.5 g (32%) of pure **6a**: mp = 113–114.5 °C; $[\alpha]^{20}_D$ = +29.2° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν 3392; 2983; 2914; 1374; 1220; 1167, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (dd, J = 5.9, 1.1 Hz, 1 H), 4.56 (dd, J = 5.8, 3.3, Hz, 1 H), 4.29 (ddd, J = 9.5, 4.3, 1.0 Hz, 1 H), 4.07 (dddd, J = 12.0, 4.3, 3.3, 1.0 Hz, 1 H), 3.84 (ddd, J = 1.1, 1.0, 1.0 Hz, 1 H), 3.08 (bd, J = 9.6 Hz, 1 H), 2.54 (bd, J = 12.1 Hz, 1 H), 1.48 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CHCl_3$) δ 110.4 (C), 78.5 (CH), 77.1 (CH), 73.3 (C), 67.8 (CH), 65.9 (CH), 63.7 (CH), 27.0 (CH_3), 24.9 (CH_3); MS (CI) m/z (rel inten) 237 (M + 1, 100), 221 (18), 161 (6), 143 (28). Anal. Calcd for $C_9H_{13}ClO_5$: C, 45.68; H, 5.54. Found: C, 45.69; H, 5.49.

(1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-1-Bromo-3,4-dihydroxy-5,6-di-*O*-isopropylidene-1,2-epoxycyclohexane (6b). 1-Bromo-2,3-dihydroxycyclohexa-4,6-diene (**4b**)[9] (4.8 g, 0.026 mol) was treated with 2,2-dimethoxypropane as described in preparation of **6a**. The resulting solution was added over the period of 20 min to the solution of $KMnO_4$ (6.20 g, 0.03 mol) and $MgSO_4$ (3.00 g, 0.025 mol) in the mixture of water (130 mL) and acetone (30 mL), precooled to −12 °C. Excess of permanganate was reduced by the addition of hydrogen sulfate, and precipitated MnO_2 was filtered off and washed with water and acetone. The filtrate was then saturated with NaCl and extracted with $CHCl_3$. Drying and evaporation of the extract under the reduced pressure yielded crude crystalline product (3.3 g), recrystallization of which (EtOAc/hexane/Et_2O) gave 1.63 g (22%) of pure **6b**: mp = 104–104.5 °C; $[\alpha]^{20}_D$ = +26.5° (*c* 1, $CHCl_3$); IR (KBr) ν 3390, 2910, 2830, 1380, 1225, 1170, 1070, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (dd, J = 5.7, 1.2 Hz, 1 H), 4.56 (dd, J = 5.7, 3.4 Hz, 1 H), 4.32

(13) (a) Lee, D. G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court Publishing Co.: La Salle, 1980; p 15. Two examples of formation of epoxy diols in low yields from permanganate oxidation of conjugated dienes not containing halogens have been reported: (a) von Rudloff, E. *Tetrahedron Lett.* **1966**, 993. (b) Sable, H. Z.; Anderson, T.; Tolbert, B.; Posternak, T. *Helv. Chim. Acta* **1963**, *46*, 1157.

(14) Ganey, M. V.; Padykula, R. E.; Berchtold, G. A. *J. Org. Chem.* **1989**, *54*, 2787.

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(16) (a) Posternak, T. *Les cyclitols*; Hermann: Paris, 1962; p 10, 283. (b) Michell, R. H.; Drummond, A. H.; Downess, C. P. *Inositol Lipids in Cell Signalling*; Academic Press: San Diego, 1989.

(17) Over 20 other diols derived from substituted aromatic compounds are commercially available from the following sources: Genencor International, Inc., Rochester, NY; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K.; Janssen Chimica, Geel, Belgium.

(18) Mass spectra were recorded on VG analytical 7070 E-HF instrument. Infrared spectra were obtained using Perkin-Elmer Model 710 B spectrophotometer. ^1H- and ^{13}C spectra were determined on Bruker WP-270 or WP-200 instruments. The optical rotation data were measured using a Perkin-Elmer 241 polarimeter.

(bdd, J = 10.1, 4.1 Hz, 1 H), 4.11 (dddd, J = 12.0, 4.9, 3.3. 1.6 Hz, 1 H), 3.91 (m, 1 H), 2.81 (d, J = 10.2 Hz, 1 H), 2.38 (d, J = 12.1 Hz, 1 H), 1.49 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 110.4 (C), 77.1 (CH), 74.0 (CH), 71.7 (C), 67.6 (CH), 66.1 (CH), 63.7 (CH), 27.1 (CH_3), 25.1 (CH_3); MS (CI) m/z (rel inten) 281 (M + 1, 100), 265 (30), 205 (12), 189 (15), 179 (10), 125 (12), 117 (15), 101 (12); calcd for $C_9H_{14}O_5Br$ (M + 1) 281.0025, Found (M + 1) 281.0074.

(1*R*,2*S*,3*S*,4*S*,5*R*,6*S*)-4,5-Dihydroxy-1,6-di-*O*-isopropylidene-2,3-epoxycyclohexane (8). Method A. The solution of **6a** (103 mg, 0.435 mmol), tris(trimethylsilyl)silane (130 mg, 0.522 mmol) and AIBN (25 mg, 0.152 mmol) in toluene (1.5 mL) was heated for 6 h under argon to 105 °C. Reaction mixture was evaporated to dryness and flash chromatography (10% deactivated silica gel, $CHCl_3$/MeOH, 95:5) of the oily product yielded 37.1 mg (42%) of 8. (When **6b** was used, the yield of 8 was 48%). **Method B.** On a larger scale **6a** (4 g, 16.9 mmol), tris-(trimethylsilyl)silane (4.72 g, 18.98 mmol), and AIBN (0.4 g, 2.44 mmol) were mixed in toluene (25 mL) and degassed with argon. The mixture was stirred at 70 °C until all material dissolved whereupon it was refluxed for 5 h. The cooled mixture was extracted with water (4×) and the combined aqueous extracts were mixed with alumina (1 g) and activated charcoal (1 g) and filtered with suction through Celite. Evaporation gave 3.37 g of a solid containing 65% of 8. This material was used as such in the hydrolysis to 1. **Method C.** The protocol used in the synthesis of (+)-pinitol was repeated and scaled up from that originaly reported.[9] Thus **4b** (20 g) yielded epoxide 8 (10.1 g) in an overall yield of 48%.

D-*chiro*-3-Inosose (3). The mixture of **6a** (93.7 mg, 0.396 mmol), Al_2O_3 (activated, basic, Brockmann I, 150 mg), and 2 mL of water was heated while stirring for 0.5 h to 80 °C, and then Al_2O_3 was filtered off and washed with water. The resulting solution was stirred with Amberlite A 21 (30 mg) for 15 min at ambient temperature, filtered, and evaporated under reduced pressure. Resulting amorphous solid was stirred for 24 h with 2-propanol. Precipitating solid was filtered and dried to give 72 mg (84%) of **3**. Pure sample was obtained by recrystallization from the mixture of water and 2-propanol: mp = 195–197 °C dec; $[\alpha]^{20}_D$ = +68.6° (c 1, H_2O); IR (KBr) ν 3346, 3006, 1735, 1576, 1420, 1302, 1132, 1078, 1005 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.29 (d, J = 3.5 Hz, 1 H), 5.16 (d, J = 3.3 Hz, 1 H), 5.01 (d, J = 6.1 Hz, 1 H), 4.91 (d, J = 5.4 Hz, 1 H), 4.72 (d, J = 6.8 Hz, 1 H), 4.41 (ddd, J = 6.6, 3.3, 1.2 Hz, 1 H), 4.16 (ddd, J = 9.3, 5.4, 1.2 Hz, 1 H), 3.93 (ddd, J = 4.1, 3.3, 3.3 Hz, 1 H), 3.83 (ddd, J = 4.1, 3.5, 3.1 Hz, 1 H), 3.58 (ddd, J = 9.4, 5.9, 3.1 Hz, 1 H); ^{13}C NMR (D_2O) δ 208.0 (C), 75.7 (CH), 74.1 (CH), 73.6 (CH), 73.3 (CH), 71.1 (CH); MS (CI) m/z (rel inten) 179 (M + 1, 18), 161 (35), 143 (100), 125 (20), 115 (12), 97 (10); calcd for $C_6H_{11}O_6$ (M + 1) 179.0556, found (M + 1) 179.0543.

D-*chiro*-Inositol (1). Method A. The mixture of **8** (9.7 g, 44.05 mmol), sodium benzoate (30 mg, 0.21 mmol), and water (150 mL) was refluxed in darkness under argon for 83 h. The reaction mixture was evaporated, dissolved in the mixture of water and methanol, and filtered with charcoal. The resulting colorless solution was evaporated to dryness to give 8.5 g (98%) of the crude product containing >95% of **1**. Recrystallization from water and ethanol furnished 6.63 g (77% overall) of pure **1**: mp = 238–242 °C (lit. 248 °C;[19] authentic sample 238–242 °C); $[\alpha]^{20}_D$ = +63.2° (c 1, H_2O) (lit. +65°, (c not given, H_2O);[19] authentic sample +57.5° (c 1, H_2O)); ^{1}H NMR (D_2O) δ 3.90 (m, 2 H), 3.62 (m, 2 H), 3.46 (m, 2 H); GCMS was identical with an authentic sample. **Method B.** The crude epoxide **8** (65% content) was similarly hydrolyzed to a mixture of inositols in which D-*chiro*-inositol content was approximately 70% in addition to 30% of *neo*-inositol, which, due to its lower solubility, was crystallized from this mixture to afford enriched title compound purified by further crystallization from water and ethanol.

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Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra of compounds **1**, **3**, **6**, and **8** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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